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EARLY ADVERSITY IN CHRONIC DEPRESSION: CLINICAL CORRELATES AND RESPONSE TO PHARMACOTHERAPY

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Abstract

Background—There is growing evidence suggesting that early adversity may be a marker for a distinct pathway to major depressive disorder (MDD). We examined associations between childhood adversity and a broad variety of clinical characteristics and response to pharmacotherapy in a large sample of patients with chronic forms of MDD.

Methods—Subjects included 808 patients with chronic forms of MDD (chronic MDD, double depression, or recurrent MDD with incomplete recovery between episodes and a total continuous duration of >2 years) who were enrolled in a 12-week open-label trial of algorithm-guided pharmacotherapy. Baseline assessments included a semi-structured diagnostic interview, and clinician- and self-rated measures of depressive symptoms, social functioning, depressotypic cognitions, and personality traits, and childhood adversity. Patients were re-evaluated every 2 weeks.

Results—A longer duration of illness; earlier onset; greater number of episodes, symptom severity, self-rated functional impairment, suicidality, and comorbid anxiety disorder; and higher levels of dysfunctional attitudes and self-criticism were each associated with multiple forms of childhood adversity. A history of maternal overcontrol, paternal abuse, paternal indifference, sexual abuse, and an index of clinically significant abuse each predicted a lower probability of remission. Among patients completing the 12-week trial, 32% with a history of clinically significant abuse, compared to 44% without such a history, achieved remission.

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Conclusions—These findings indicate that a history of childhood adversity is associated with an especially chronic form of MDD that is less responsive to antidepressant pharmacotherapy.

Keywords

major depression; mood disorders; childhood maltreatment; clinical features; treatment response

INTRODUCTION

Early adversity plays an important role in the development and course of major depressive disorder (MDD).^[1-3] Numerous studies have documented associations between MDD and retrospective reports of parental indifference, overcontrol, and physical and sexual abuse.^[4,5] Although findings from retrospective studies must be regarded cautiously,^[6] depressed persons' reports of childhood adversity are stable despite changes in clinical state and over periods of up to 20 years.^[7,8] Furthermore, adults' retrospective reports of childhood adversity are often corroborated by informants or records.^[6,9] Moreover, several prospective studies have reported associations between childhood maltreatment and later MDD.^[10,11] Finally, twin studies indicate that genetic factors cannot explain the association between early adversity and MDD.^[12]

MDD is a heterogeneous condition that probably results from multiple etiological processes and developmental pathways. Early adversity is likely to be an important link in one of these pathways, and may be a marker for a subtype of MDD.^[2,3] Many studies have attempted to delineate this subtype by examining associations between early maltreatment and specific clinical features. Childhood adversity is associated with an earlier onset,^[13,14] greater number of episodes,^[13,15] more chronic course,^[15-18] higher levels of depressotypic cognitions,^[11] and greater suicidality.^[10,19] Several studies have found an association between childhood sexual abuse and atypical features,^[20,21] however there are conflicting findings for melancholic features.^[19,22]

Studies have also examined the relationship between early adversity and neurobiological and psychosocial correlates of depression. Depressed patients with a history of maltreatment exhibit greater hypothalamic–pituitary–adrenal axis and autonomic reactivity to laboratory stressors and pharmacological challenges,^[23] and have smaller hippocampal volumes^[24] than depressives without a history of maltreatment. Moreover, several studies have reported that early adversity moderates the association between stress and subsequent depressive symptoms, such that patients with a history of adversity are more sensitive to the effects of life stressors.^[25-27] Finally, childhood maltreatment may influence treatment response. Nemeroff et al.^[28] found that a greater proportion of chronically depressed outpatients with a history of early adversity achieved full remission with a form of cognitive–behavioral psychotherapy than pharmacotherapy, whereas patients without such a history had a nonsignificantly better response to pharmacotherapy. Barbe et al.^[29] reported that cognitive therapy and supportive therapy were equally efficacious for depressed adolescents with a history of sexual abuse, but cognitive therapy was superior among youths with no history of abuse.

We examined whether childhood adversity is associated with clinical features and treatment response in a large sample of patients with chronic forms of MDD. This is a particularly relevant population because rates of childhood maltreatment are higher in chronic than nonchronic depression,^[18] and some of the strongest evidence for an early adversity-based subtype has been reported in chronic samples.^[25,28] Unlike many past studies, which were limited to a small number of clinical features and/or a single form of maltreatment (e.g. sexual abuse), we examined a variety of clinical features and forms of adversity. In addition,

we explored whether early adversity predicts response to algorithm-guided pharmacotherapy designed to reflect optimal clinical practice.

MATERIALS AND METHODS

SUBJECTS

The sample was 808 outpatients (see Table 1) recruited from eight academic centers through clinician referrals (8.3%) and other sources (e.g. advertising, self-referral, referral by friends/family; 91.7%). Patients had a current DSM-IV major depressive episode (MDE) of 4 weeks duration and significant depressive symptoms that had persisted for >2 years without periods of remission. Subjects met criteria for double depression, chronic MDE, or recurrent MDD with incomplete recovery between episodes with a total continuous duration of >2 years. Patients were between ages 18 and 75, English speaking, and had a 24-item Hamilton Depression Rating Scale (HAM-D)^[30] score at intake 20.

Exclusion criteria were pregnancy; current psychotic disorder; history of bipolar disorder; dementia; principal diagnosis of posttraumatic stress disorder, anorexia or bulimia nervosa, or obsessive-compulsive disorder; antisocial, schizotypal, or severe borderline personality disorder; and current alcohol or other substance dependence disorder (except nicotine).

Patients who had failed four treatment steps in the pharmacotherapy algorithm, were unwilling to terminate other forms of treatment, or had an unstable or terminal medical illness that would compromise participation were excluded. After complete description of the study to subjects, written informed consent was obtained.

ASSESSMENTS

Diagnoses—Diagnostic data were obtained at baseline using the Structured Clinical Interview for DSM IV (SCID).^[31] Inter-viewers were experienced raters who had been certified in the SCID by an expert rater at another site based on a videotaped interview.

Depression severity—The severity of depressive symptoms was assessed at baseline and on a biweekly basis throughout the study using the HAM-D.^[30] It was administered by experienced raters who were certified on an annual basis by independently rating videotapes of criterion evaluations. The Inventory of Depressive Symptoms, self-report version (IDS-SR)^[32] served as a secondary measure of baseline severity.

Impairment—Baseline psychosocial functioning was assessed with the Longitudinal Interval Follow-Up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT).^[33] The LIFE-RIFT is a semi-structured interview assessing functioning in the areas of work, interpersonal relationships, and leisure activities. The Social Adjustment Scale, self-report version (SAS-SR)^[34] served as a secondary measure of impairment.

Cognitive/personality styles—Given evidence that early adversity is associated with depressive cognitive and personality styles,^[1,3] patients completed the Dysfunctional Attitudes Scale^[35] and the Depressive Experiences Questionnaire self-criticism and dependency scales.^[36]

Early adversity—At baseline, patients completed the Measure of Parental Style (MOPS),^[37] which assesses parents' behavior toward the patient through age 16. The MOPS includes three scales for each parent: indifference (six items assessing ignoring, rejecting, being uncaring of, being uninterested in, and forgetting about the respondent, and leaving the respondent on their own); overcontrol (four items assessing being overcontrolling,

overprotective, and critical of the respondent, and making the respondent feel guilty); and abuse (five items assessing physical abuse, verbal abuse, unpredictable behavior, making the respondent feel unsafe, and making the respondent feel in danger). These items were rated on a four-point scale ranging from “not at all true” to “extremely true”. As the MOPS does not assess sexual abuse, we used the five-item sexual abuse subscale from the short-form of the Childhood Trauma Questionnaire.^[38] The items include being touched or made to touch someone else in a sexual way, forced through threats or lies to engage in sexual behavior, made to do or watch sexual things, molested, and sexually abused. Items were scored on a five-point scale ranging from “never true” to “very often true”.

The internal consistency (coefficient α) of the scales in our sample ranged from .73–.94 (median = .90). Correlations between the three maternal MOPS scales ranged from .32–.68 (median = .59), and correlations between the three paternal MOPS scales ranged from .31–.64 (median = .59). Correlations of the maternal scales with the paternal scales ranged from .16–.39 (median = .25). Correlations of the six MOPS scales with the sexual abuse scale ranged from .17–.33 (median = .23).

To facilitate clinical decision-making, we created a dichotomous variable to denote “clinically significant abuse.” This was scored present if any of the following four items was endorsed: mother physically violent or abusive; father physically violent or abusive; molested; or sexually abused, at one of the two highest points on the item’s response scale. The proportion of the sample endorsing each of these items ranged from 11–18%; 36% of patients experienced at least one item.

PHARMACOTHERAPY

Patients received up to 12 weeks of algorithm-guided open-label pharmacotherapy. The selection and sequence of medications was based on an algorithm developed from treatment guidelines and previous studies such as the Texas Medication Algorithm Project.^[39] The sequence consisted of: sertraline, escitalopram, bupropion XL, venlafaxine XR, and mirtazapine. The initial medication was selected based on prior history of response. Thus, unless patients had a history of intolerance or nonresponse to an adequate trial, they received sertraline. Patients with a history of intolerance or nonresponse to an adequate trial of sertraline received escitalopram, and so forth. The protocol specified minimum and maximum doses, speed of dosage escalation, and adequate trial lengths. Patients were evaluated bi-weekly. If side effects were unacceptable, the dosage could be decreased. If the patient had not achieved an adequate response and was tolerating the medication, the dose could be increased. If the patient was intolerant to a medication during the first 4 weeks, s/he was moved to the next level of the sequence. Patients who failed to respond by week 6 were switched to the next step in the algorithm. If patients continued to meet criteria for MDD and had <30% reduction on the HAM-D for two consecutive assessments after week 6, they were removed from this phase of the study. The study was registered on clinicaltrials.gov (URL: <http://www.clinicaltrials.gov>; registration number NCT00057551).

DATA ANALYSIS

First, we examined bivariate associations between the early adversity variables and six demographic variables (age, sex, race, Hispanic ethnicity, education (high school or less versus at least some college), and marital status (not married versus married)); 10 clinical variables (baseline HAM-D; baseline IDS-SR; duration of index MDE; age of onset of earliest depressive disorder (MDD or dysthymic disorder); duration of illness (current age–age of onset); lifetime number of MDEs; melancholic subtype; atypical subtype; lifetime anxiety disorder; and lifetime substance use disorder); two measures of functional

impairment (LIFE-RIFT and SAS-SR total scores); and three cognitive/personality variables (dysfunctional attitudes, self-criticism, and dependency).

Bivariate associations between continuous measures were examined using Spearman correlations; associations between a continuous and a categorical measure used point-biserial correlations; and associations between two categorical variables used ϕ -coefficients. Due to the large number of variables, α was set at $P < .01$ (although trends at $P < .05$ are reported). Due to missing data, N 's varied from 591 to 792.

To determine which variables were uniquely associated with each form of adversity, we conducted backwards stepwise multiple linear and logistic regression analyses. To minimize multicollinearity, only the interview (not self-report) measures of depression severity and impairment were included. Age was also excluded because it is a function of age of onset and duration of illness. Alpha was set at $P < .05$. Due to listwise deletion, N 's ranged from 440 to 511.

Associations between adversity and pharmacotherapy response were examined using mixed effects logistic regression models, with remission status (17-item HAM-D < 8) at each assessment point as the dependent variables. Separate models were estimated for each of the eight adversity variables, with adversity, time, and the adversity $\times$ time interaction as independent variables. N 's ranged from 653 to 747.

RESULTS

At baseline, 293 patients (36.3%) had a chronic MDE, 249 (30.8%) had a recurrent nonchronic MDE with incomplete inter-episode recovery and a total continuous duration of > 2 years, 105 (13.0%) had a nonchronic MDE superimposed on dysthymic disorder, and 161 (19.9%) had a chronic MDE superimposed on dysthymic disorder. Of the patients, 619 (76.8%) entered the study at stage 1 of the algorithm (sertraline); 92 (11.4%) entered at stage 2 (escitalopram), 63 (7.8%) entered at stage 3 (buprion XL), 30 (3.7%) entered at stage 4 (venlafaxine XR), and 2 patients (0.3%) entered at stage 5 (mirtazapine). Neither study diagnosis nor algorithm stage at entry was associated with any of the early adversity variables, hence they are not considered further.

BIVARIATE CORRELATIONS

Female gender, nonwhite race, Hispanic ethnicity, and lower education were associated with sexual abuse (Table 1). Female gender was also associated with adverse maternal behaviors (indifference, overcontrol, and abuse) but not with adverse paternal behavior. No other demographic variable was significantly associated with early adversity.

Three clinical variables were associated with all forms of childhood maltreatment: longer duration of illness, earlier age of onset, and self-reported functional impairment. Interview- and self-rated depression severity, number of MDEs, history of suicide attempts, and lifetime anxiety disorders were also associated with multiple forms of adversity. The melancholic and atypical subtypes and history of substance use disorder were not associated with any form of maltreatment. Of the cognitive/personality measures, self-criticism and dysfunctional attitudes were associated with multiple types of adversity, but dependency was not correlated with any maltreatment variables.

Each form of adversity was associated with multiple demographic, clinical, and cognitive/personality variables. Importantly, when adversity was limited to clinically significant abuse, these associations were not diminished.

MULTIVARIATE ANALYSES

The significant effects in the multiple regression models appear in Table 2. Duration of illness had significant unique effects in five of the seven models. Gender, dysfunctional attitudes, and self-criticism made significant unique contributions to four models, and race was uniquely associated with three forms of maltreatment. Hispanic ethnicity, education, duration of the index episode, age at onset, suicidality, history of anxiety disorder, impairment, and dependency had more specific effects, accounting for unique variance in only one form of adversity.

Seven variables were uniquely associated with clinically significant abuse. These included female gender (OR = 1.917; 95% CI = 1.263–2.909, $P=.002$), non-white race (OR = .531; 95% CI = 0.295–0.955, $P<.04$), Hispanic ethnicity (OR = 2.226; 95% CI = 1.052–4.710, $P<.04$), less education (OR = 0.608; 95% CI = 0.403–0.916, $P<.02$), duration of index MDE (OR = 1.002; 95% CI = 1.000–1.004, $P<.03$), duration of illness (OR = 1.022; 95% CI = 1.005–1.038, $P<.01$), and dysfunctional attitudes (OR = 1.006; 95% CI = 1.000–1.012, $P<.04$).

Duration of illness was the one variable associated with almost all forms of maltreatment in both the bivariate and multivariate analyses. Therefore, we explored these associations from another perspective, examining which forms of adversity had unique associations with duration of illness. We conducted a multiple linear regression analysis in which the six MOPS scales and sexual abuse were entered simultaneously as independent variables and duration of illness was the dependent variable. Three MOPS scales had significant unique associations with duration of illness: maternal abuse ($B = .458$; SE = .214; $t = 2.14$, $P=.03$), maternal indifference ($B = .356$; SE = .157; $t = 2.27$, $P=.02$), and paternal overcontrol ($B = .472$; SE = .214; $t = 2.20$, $P<.03$).

TREATMENT RESPONSE

Of the 808 patients, 652 (80.7%) completed at least 8 weeks of treatment and 479 (59.3%) completed all 12 weeks. Maternal overcontrol, paternal abuse, paternal indifference, sexual abuse, and clinically significant abuse predicted a significantly lower probability of remission at any given time point (Table 3). The main effect of time was significant in each model, reflecting increasing remission rates over time. In addition, there was a significant clinically significant abuse by time interaction, indicating that the probability of remission increased significantly faster over time for patients without a history of clinically significant abuse compared to those with such a history (Fig. 1).

We conducted several subsidiary analyses to further examine the association between early adversity and treatment response, focusing particularly on clinically significant abuse. First, clinically significant abuse was not related to the probability of dropping out before week 12. Second, all but one of the significant effects remained significant when lifetime anxiety and substance use disorders were included as covariates in the models (the exception was maternal overcontrol, which dropped to $P=.059$). Third, lifetime anxiety disorder, substance use disorder, and, more specifically, posttraumatic stress disorder, did not moderate the association between clinically significant abuse and remission over time. Fourth, as most patients were treated with sertraline, we repeated the analysis for patients who started and completed the trial on sertraline. The magnitude of the clinically significant abuse $\times$ time interaction was identical to the full sample, although the P -value dropped to .06 due to the smaller sample. Finally, for patients on sertraline, the final dose of medication (mean = 128.9; SD = 62.8 mg) did not moderate the association between clinically significant abuse and remission.

DISCUSSION

Consistent with previous research we found that a substantial proportion of chronically depressed patients (36%) experienced clinically significant abuse during childhood.^[15-18,28] We examined associations between multiple forms of early adversity and a large array of demographic, clinical, and cognitive/personality variables and response to pharmacotherapy in a large sample of patients with chronic forms of MDD. First, we consider associations with baseline characteristics, and then discuss prediction of treatment response.

Duration of illness was associated with all forms of maltreatment in bivariate analyses, and was uniquely associated with most types of adversity in multivariate analyses that included the other predictors. When the various forms of maltreatment were entered into a simultaneous regression, duration of illness was uniquely predicted by maternal abuse, maternal indifference, and paternal overcontrol. These findings are striking as the sample was selected for chronic depression and had a mean duration of illness of 20 years. Thus, even within a highly chronic sample that excluded primary PTSD, childhood adversity is associated with a longer duration of illness. This is consistent with previous reports of an association between childhood maltreatment and chronic depression,^[15-18] and indicates that chronicity is one of the most robust correlates of early adversity in MDD.

Other variables associated with multiple forms of adversity included earlier onset, more episodes, and greater severity of symptoms, self-rated impairment, suicidality, lifetime anxiety disorder, and levels of dysfunctional attitudes and self-criticism. These results are consistent with previous reports of associations between childhood maltreatment and early onset,^[13,14] recurrent episodes,^[13,15] suicidality,^[10,19] and depressotypic cognitive/personality styles.^[1]

Early adversity was not associated with the symptom-based subtypes of melancholic and atypical depression. The literature on melancholia is conflicting,^[19,22] and the results might differ using narrower criteria than those in DSM-IV. Several studies have reported associations between sexual abuse and atypical depression.^[20,21] As these studies included nonchronic patients, the discrepant results may be due to sample differences.

Associations with adversity were stronger for self-than clinician-rated measures of severity and impairment. As adversity was self-rated, it is likely that shared method variance inflated associations with the self-report measures.

We also explored whether early adversity predicted response to antidepressant pharmacotherapy. A history of maternal overcontrol, paternal abuse, paternal indifference, sexual abuse, and our index of clinically significant abuse each predicted a lower probability of remission during a 12-week course of algorithm-guided pharmacotherapy. In addition, there was a significant interaction between clinically significant abuse and time, indicating that the gap in remission rates between patients with and without a history of abuse increased as treatment continued. Indeed, of patients completing the 12-week trial, only 32% with a history of clinically significant abuse remitted, compared to 44% of patients without such a history. The difference in remission rates was greatest in the latter weeks of the trial. Patients without a history of maltreatment derived increasing benefit from continued treatment, whereas the rate of remission increased more slowly in patients with a history of adversity, perhaps reflecting the presence of a medication-resistant subgroup that requires other treatment modalities.

Surprisingly few studies have examined the association between early adversity and response to pharmacotherapy. Our findings are broadly consistent with Nemeroff et al.^[28] who reported that among patients receiving pharmacotherapy, those with a history of early

adversity had a nonsignificantly lower remission rate than those without such a history. They also found that patients with a history of adversity were significantly more likely to remit with psychotherapy than pharmacotherapy. This is consistent with the possibility that childhood maltreatment and other early stressors may comprise a pathway to chronic depression for a subgroup of patients, who may be more responsive to psychosocial interventions.^[9,23,25] As we did not include a psychotherapy condition, we could not determine whether patients with a history of maltreatment are more responsive to psychosocial interventions. However, we plan to explore this issue in the second phase of this study, in which a subset of partial and nonresponders to pharmacotherapy are randomized to receive psychotherapy augmentation.

It is interesting to speculate about mechanisms mediating the associations of childhood adversity with chronicity and poor medication response. Early adversity is associated with dysregulation of neurobiological stress response systems and the development of interpersonal difficulties and depressotypic cognitive schemas.^[3,23,25] These factors may maintain depression and require psychosocial treatments that directly target maladaptive coping, interpersonal, and cognitive patterns.^[28]

This study had a number of strengths, including a large, carefully evaluated sample; numerous baseline demographic, clinical, and cognitive/personality predictors and forms of early adversity; and a prospective clinical trial designed to optimize treatment response. The flexible treatment choices provide greater generalizability than treatment with a single antidepressant as they better approximate community-based care. However, the study also had several limitations. First, adversity was assessed retrospectively and the associations between adversity and baseline characteristics were cross-sectional. As reviewed above, the influence of clinical state on retrospective ratings of adversity appears to be minimal. Nonetheless, a prospective design would afford greater confidence. Second, the strength of the associations was modest, perhaps due to the homogeneity of the sample, all of whom had chronic forms of MDD. Third, the findings may not generalize to nontreatment seeking and nonchronically depressed samples. Finally, although we attempted to minimize exclusion criteria, patients with some co-occurring psychiatric and general medical conditions were not included; hence the results may not generalize to a population with these comorbidities.

CONCLUSION

These findings suggest that early adversity may play an important role in a subgroup of MDD patients with an early onset, chronic course, self-criticism, dysfunctional attitudes, lifetime anxiety, suicidality, and poor response to pharmacotherapy. These results support the need for work on the processes through which adversity increases risk for the onset and maintenance of MDD and interventions targeted at depressed individuals with a history of childhood maltreatment.

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Ham-17 Remission by Week and Clinically Significant Abuse

Figure 1.

Proportion of patients with and without a history of clinically significant abuse who achieved remission at each biweekly assessment during the course of the study.

TABLE 1
Means/percents and bivariate associations for early adversity and demographic, clinical, and personality variables

Variable	Maternal indifference	Maternal overcontrol	Maternal abuse	Paternal indifference	Paternal overcontrol	Paternal abuse	Sexual abuse	Clin significant abuse	% or M (SD)
Age	.05	.01	.02	.06	-.01	.03	.01	-.01	43.6 (12.4)
Sex (female)	.21**	.13**	.20**	-.02	-.03	-.02	.25**	.17**	55.0%
Race (white)	-.07 ⁺	-.08 ⁺	-.04	.02	-.03	.00	-.14**	-.08 ⁺	86.2%
Hispanic ethnicity	.03	.04	.07	.00	.02	-.01	.11*	.08 ⁺	7.6%
Education (>high school)	-.08 ⁺	.07	-.00	-.02	.03	-.05	-.11*	-.09 ⁺	61.0%
Marital status (married)	-.00	-.03	.03	-.04	-.08 ⁺	-.03	.05	-.00	40.6%
Duration illness (yrs)	.25**	.25**	.27**	.23**	.19**	.22**	.11*	.19**	19.7 (13.8)
Duration index MDE (mos)	.09 ⁺	.04	.07 ⁺	.08 ⁺	.09 ⁺	.08 ⁺	.04	.14**	84.0 (105.4)
Number MDEs	.11*	.11*	.13*	.10*	.06	.07	.03	-.01	2.4(2.8)
Age onset MDD or DYS	-.22**	-.25**	-.27**	-.19**	-.23**	-.23**	-.10*	-.19**	23.7 (13.4)
Baseline 24-item HAM-D	.09 ⁺	.10*	.10*	.06	.12*	.14**	.08 ⁺	.15**	27.9 (5.9)
Baseline IDS	.10*	.11*	.12*	.11*	.10 ⁺	.16**	.18**	.21**	37.9 (10.1)
Melancholia	.06	.07	.06	.01	.05	.06	.04	.05	52.4%
Atypical depression	.02	.02	.04	.02	-.04	-.02	.03	.01	15.1%
History suicide attempts	.19**	.13**	.17**	.12*	.05	.06	.19**	.13**	11.0%
History anxiety disorder	.09 ⁺	.15**	.10*	.04	.12*	.07 ⁺	.11*	.13**	44.5%
History substance disorder	.00	.02	.03	.08 ⁺	.07	.09 ⁺	-.00	.02	41.3%
LIFE-RIFT	.04	.05	.03	.04	.10*	.06	.12*	.13**	14.6 (2.5)
SAS-SR	.15**	.13**	.11*	.15**	.13**	.15**	.12**	.19**	2.5 (0.5)
Dysfunctional attitudes	.05	.17**	.09 ⁺	.16**	.12*	.11*	.04	.07	144.0 (35.5)
Self-criticism	.13**	.23**	.15**	.23**	.10 ⁺	.18**	.05	.13*	.98 (0.8)
Dependency	-.10 ⁺	.09 ⁺	-.01	-.07	.07	.00	.02	-.02	-0.6 (0.8)
Mean or %	3.68	4.87	2.98	5.66	3.76	3.47	2.89	35.9%	-

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Variable	Maternal indifference	Maternal overcontrol	Maternal abuse	Paternal indifference	Paternal overcontrol	Paternal abuse	Sexual abuse	Clin significant abuse	% or M (SD)
Standard deviation	4.79	3.54	4.06	5.59	3.25	4.42	5.32	-	-

[†] $P<.05$
^{*} $P<.01$
^{**} $P<.001$.

TABLE 2
Significant multivariate associations between early adversity and demographic, clinical, and personality variables

Variable	Maternal indifference B (SE)	Maternal overcontrol B (SE)	Maternal abuse B (SE)	Paternal indifference B (SE)	Paternal overcontrol B (SE)	Paternal abuse B (SE)	Sexual abuse B (SE)
Sex (female)	1.585 (.407) ***	1.051 (.301) ***	1.678 (.327) ***	-	-	-	2.175 (.417) ***
Race (white)	-1.227 (.588) *	-.908 (.440) *	-	-	-	-	-1.976 (.599) **
Hispanic ethnicity	-	-	1.574 (.643) *	-	-	-	-
>high school education	-.921 (.406) *	-	-	-	-	-	-
Marital status (married)	-	-	-	-	-	-	-
Duration illness	.074 (.015) ***	.050 (.011) ***	.070 (.012) ***	.084 (.018) ***	-	.072 (.014) **	-
Duration index MDE	-	-	-	-	.004 (.001) ***	-	.004 (.002) ***
Number MDEs	-	-	-	-	-	-	-
Age onset MDD/DYS	-	-	-	-	-.049 (.012) ***	-	-
Baseline HAM-D	-	-	-	-	-	-	-
Melancholia	-	-	-	-	-	-	-
Atypical depression	-	-	-	-	-	-	-
Hx suicide attempts	1.655 (.660) *	-	-	-	-	-	3.024 (.680) **
Hx anxiety disorder	-	.701 (.302) *	-	-	-	-	-
Hx substance disorder	-	-	-	-	-	-	-
LIFE-RIFT	-	-	-	-	-	-	.224 (.080) **
Dysfunctional attitudes	-	.014 (.005) **	-	.034 (.009) ***	.012 (.004) **	.020 (.006) ***	-
Self-criticism	.814 (.275) **	.542 (.236) *	.744 (.223) ***	.998 (.390) **	-	-	-
Dependency	-	-	-	-.970 (.362) **	-	-	-

Note: All demographic and clinical predictors were entered into a backwards stepwise linear regression model for each adversity variable.

* $P < .05$

** $P < .01$

*** $P < .001$.

TABLE 3
Early adversity and remission (17-item Hamilton depression rating scale scores < 8) over the course of acute-phase treatment

	Time (weeks)											
	0 OR	2 OR	4 OR	6 OR	8 OR	10 OR	12 OR					
Maternal indifference	1.03	1.02	1.02	1.01	1.01	1.00	1.00					
Maternal overcontrol [*]	.99	.98	.97	.96	.95	.94	.93					
Maternal abuse	1.00	0.99	0.99	0.98	0.98	0.97	0.96					
Paternal indifference [*]	.99	.98	.98	.97	.96	.96	.95					
Paternal overcontrol [†]	1.01	1.00	0.98	0.97	0.96	0.95	0.94					
Paternal abuse ^{**}	1.00	0.99	0.98	0.97	0.95	0.94	0.93					
Sexual abuse ^{**}	.99	.98	.97	.97	.96	.95	.94					
Clinically significant abuse ^{***†}												
No	0.03	0.06	0.10	0.18	0.31	0.56	1.00					
Yes	.02	.03	.06	.10	.17	.33	.52					

Main effect

Two-way interaction with adversity measure and time

Note: The main effect for time was highly statistically significant in each model at $P < .0001$. The odds ratios indicate a relative change in the odds of remission associated with a one-point increase in the early adversity variable. Clinically significant abuse is scored present/absent; its presence is associated with a decrease in the probability of remission at any given assessment. The N 's in these analyses ranged from 653 to 747, and the number of observations ranged from 3220 to 3656.

[†] P -value < .10

^{*} P -value < .05

^{**} P -value < .01.

[†] P -value < .05.